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Changes in Hepatic Lobar Function After Right Portal Vein Embolization

An Appraisal by Biliary Indocyanine Green Excretion

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Objective
The changes in the functional capacity of the hepatic lobe after right portal vein embolization (RPE) were investigated in patients with complete obstruction of the hepatic hilus who had undergone multiple percutaneous transhepatic biliary drainage catheterizations.

Methods
After injection of 0.5 mg/kg of indocyanine green (ICG), bile draining from each hepatic lobe was collected separately for 6 hours. Biliary ICG excretion in each hepatic lobe was estimated and compared with hepatic lobar volume measured by computed tomographic volumetry before and an average of 11 days after RPE.

Results
Right portal vein embolization produced a significant increase in bile volume and biliary ICG concentration in the left lobe, resulting in a significant increase in ICG excretion in the left lobe. The percentage of ICG excretion in the left lobe to the whole-liver excretion showed a mean increase of 20.1%, which was statistically significant. In contrast, the percentage of left lobar volume to the total liver volume increased by only 8.3%.

Conclusions
Measurement of biliary ICG excretion is useful for estimating changes of hepatic lobar function and has revealed that within 11 days RPE enhances functional capacity in the left lobe compared with volume gain without affecting total liver function.

With advances in diagnostic imaging and surgical techniques, extensive liver resection and hepatopancreatoduodenectomy, with or without portal vein resection and reconstruction, have been performed for biliary tract carcinoma.[1–6] Such aggressive operations, however, carry high morbidity and mortality rates following posthepatectomy liver failure.[2,4–7] To prevent this fatal complication, preoperative portal vein embolization has recently been used.[8–12] Portal vein embolization induces atrophy of the corresponding lobe together with contralateral hypertrophy. Although lobar volume changes can be determined easily with use of volumetric methods using computed tomography,[13] alteration of lobar function in proportion to volume

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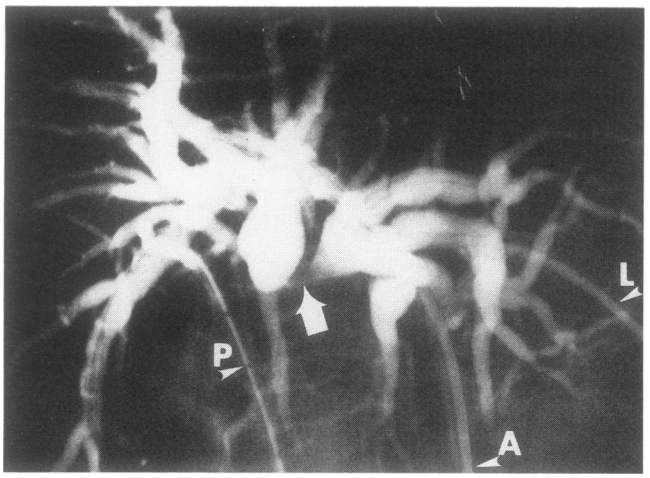

Figure 1. Cholangiogram through biliary drainage catheters showing complete obstruction of the hepatic hilus (arrow). Three catheters were placed in the left hepatic lobe (L), right anterior segment (A), and right posterior segment (P), respectively.

change remains poorly understood, because we cannot accurately estimate hepatic lobar function. To clarify this issue, we measured biliary indocyanine green (ICG) excretion in patients with complete obstruction of the hepatic hilus who had undergone biliary drainage. In this study, special attention was paid to the changes in functional capacity of each hepatic lobe after portal vein embolization in patients with biliary tract cancer.

METHODS

Subjects

This study involved eight patients with malignant biliary obstruction of the hepatic hilus who underwent right portal vein embolization (RPE) as preoperative management for extensive liver resection at Nagoya University Hospital. We used the ipsilateral approach to perform RPE using our device with fibrin glue (Beriplast P; Hoechst, Tokyo, Japan) and iodized oil (Lipiodol; Kodama Pharmaceutical Co., Tokyo, Japan) as the embolic material.[10] The study group consisted of four men and four women with an average age of 59.3 years (range, 44–72 years). Four patients had diabetes mellitus. The causes of biliary obstruction were advanced gallbladder carcinoma involving the hepatic hilus in four patients and hilar bile duct carcinoma in four patients. These eight patients, all of whom had a complete obstruction of the hepatic hilus without any communication between the hepatic lobes, had jaundice on admission. However, none had jaundice at the time of the ICG test after percutaneous transhepatic biliary drainage. To drain the entire biliary system, we performed multiple percutaneous transhepatic biliary drainage catheterizations (Fig. 1)[14]: two catheters were placed in two patients, three catheters in two patients, four catheters in one patient, and five catheters in three patients. Written informed consent for participation was obtained from each patient before enrollment in the study, which was approved by the human research review committee of the Nagoya University Hospital.

Indocyanine Green Test

The pharmacokinetics of ICG were studied before and 10 to 16 days (mean, 11.3 days) after RPE. After fasting overnight, the patients were injected with freshly dissolved ICG (0.5 mg/kg of body weight) (Dai-ichi Pharmaceutical Co., Tokyo) through the antecubital vein. Blood samples were drawn from the antecubital vein in the opposite arm before and 5, 10, 15, 20, 30, 40, 50, and 60 minutes after injection. Bile draining from the tight-fitting percutaneous transhepatic biliary drainage catheters was collected separately every 10 minutes for 6 hours. The distal end of the catheter was placed 50 cm below the patient, so that the bile was collected under slightly negative pressure. After measurement of bile volume, plasma and bile samples were centrifuged at 3000 rpm for 10 minutes. The supernatant was diluted with distilled water and analyzed immediately for ICG concentration using a spectrophotometer (Clinical Spectrophotometer 105-50, Hitachi, Tokyo, Japan) at 805 nm. Calibration was performed with use of control blood and bile taken before the administration of ICG.

The plasma disappearance rate (K_{ICG}), which has been commonly used clinically, was calculated by linear regression analysis of the plasma ICG concentrations at 5, 10, and 15 minutes. In addition, plasma disappearance curves were analyzed by a two-compartment open model in which compartment 1 was the plasma and compartment 2 was the liver. Elimination occurs from compartment 2 into the bile. The transfer rate constants K_{12} (rate constant from the plasma to the liver), K_{21} (rate constant from the liver to the plasma), and K_{el} (rate constant for elimination) were calculated as reported by Kawasaki et al.[15]

Maximum biliary ICG concentration (C_{max}) and the corresponding time (T_{max}) were determined from biliary ICG concentration curves. Biliary ICG excretion for 6 hours was calculated by summing excretion every 10 minutes. Excretion was computed as the biliary concentration multiplied by bile volume. Excretion of ICG was expressed as a percentage of excreted ICG to the injected dosage, because the dosage was different for each patient.

Computed Tomography Volumetry of the Liver

Computed tomography estimation of liver volume was performed before and 9 to 14 days (mean, 11.5 days)

Table 1. CHANGES IN TOTAL LIVER FUNCTION AND VOLUME AFTER RPE

	Before RPE	After RPE	p Value
Pharmacokinetic parameters of ICG			
K_{ICG} (min^{-1})	0.146 ± 0.042	0.177 ± 0.039	NS
K_{12} (min^{-1})	0.1329 ± 0.0340	0.1478 ± 0.0277	NS
K_{21} (min^{-1})	0.0065 ± 0.0017	0.0067 ± 0.0015	NS
K_{el} (min^{-1})	0.0235 ± 0.0126	0.0256 ± 0.0142	NS
Bile volume (mL)	94.9 ± 24.5	101.9 ± 31.3	NS
ICG_{ex} (%)	43.5 ± 17.3	47.1 ± 16.4	NS
Liver volume (cm^3)	1127 ± 219	1178 ± 162	NS

RPE = right portal vein embolization: ICG = indocyanine green; K_{ICG} = plasma disappearance rate of indocyanine green; K_{12} = rate constant from the plasma to the liver; K_{21} = rate constant from the liver to the plasma; K_{el} = rate constant for elimination; ICG_{ex} = 6-hour biliary indocyanine green excretion; NS = not significant.
Values expressed as mean ± standard deviation.

after RPE. Serial transverse scans at 1-cm intervals were performed from the dome to the most caudal aspect of the liver. Each slice of the liver was traced with the cursor, and the corresponding area was calculated by computer. The middle hepatic vein and gallbladder were used as landmarks on the computed tomography images to indicate the borderline between the right and left lobes.

Statistical Analysis

Results were expressed as the mean ± SD. Statistical analysis was performed with the Wilcoxon test and the Mann–Whitney test, where appropriate. A probability level of less than 0.05 was considered statistically significant.

RESULTS

Changes in Total Liver Function and Volume

According to the pharmacokinetic analysis of plasma ICG disappearance curves, K_{ICG} and K_{12} increased considerably but not significantly, from 0.146 ± 0.042 $minutes^{-1}$ before RPE to 0.177 ± 0.039 $minutes^{-1}$ after RPE and from 0.1329 ± 0.0340 $minutes^{-1}$ to 0.1478 ± 0.0277 $minutes^{-1}$, respectively. K_{21} and K_{el} did not change significantly after RPE (Table 1). Total bile volume, total ICG excretion for 6 hours, and whole-liver volume exhibited no significant change after RPE.

Changes in Biliary Indocyanine Green Concentration Curves

In all subjects, biliary ICG concentration curves against time in each hepatic lobe exhibited a parabolic pattern before and after RPE. Before RPE, ICG concentrations in the right lobe were higher at all times compared with the left lobe (significant differences were present from 30 minutes to 180 minutes after ICG injection). After RPE, however, this trend was reversed (significant differences were observed from 90 minutes to 120 minutes after injection) (Fig. 2).

C_{max} and T_{max} in each hepatic lobe were estimated and analyzed: in the right lobe, C_{max} (before RPE, 21.7 ± 9.3 mg/dL; after RPE, 19.6 ± 5.2 mg/dL) and T_{max} (before RPE, 139 ± 35 minutes; after RPE, 153 ± 36 minutes) exhibited no significant changes. However, in the left lobe, C_{max} was significantly increased from 14.8 ± 8.0 mg/dL to 22.8 ± 9.7 mg/dL ($p < 0.05$), and T_{max} was significantly shortened from 165 ± 44 minutes to 138 ± 42 minutes ($p < 0.05$).

Changes in Hepatic Lobar Function and Volume

Although bile volume for 6 hours in the right lobe exhibited no significant changes after RPE (before, 57.8 ± 16.1 mL; after, 54.3 ± 22.9 mL), bile volume in the left lobe was significantly increased, from 37.1 ± 9.6 mL to 47.7 ± 11.5 mL ($p < 0.05$). The calculated ICG excretion in the right lobe was decreased considerably but not significantly, from 31.1 ± 17.1% before RPE to 22.3 ± 13.7% after RPE. Excretion of ICG in the left lobe was significantly increased, from 15.2 ± 6.4% to 24.6 ± 7.5% ($p < 0.05$). The right lobar volume significantly decreased from 718 ± 177 cm^3 before RPE to 641 ± 110 cm^3 after RPE ($p < 0.05$). However, the left lobar volume significantly increased from 385 ± 70 cm^3 to 504 ± 105 cm^3 ($p < 0.05$) (Fig. 3).

To establish the relationship between the functional capacity and volume of the left (nonembolized) lobe, we calculated the following two parameters: L_{ICG}, defined as the percentage of ICG excretion in the left lobe to the

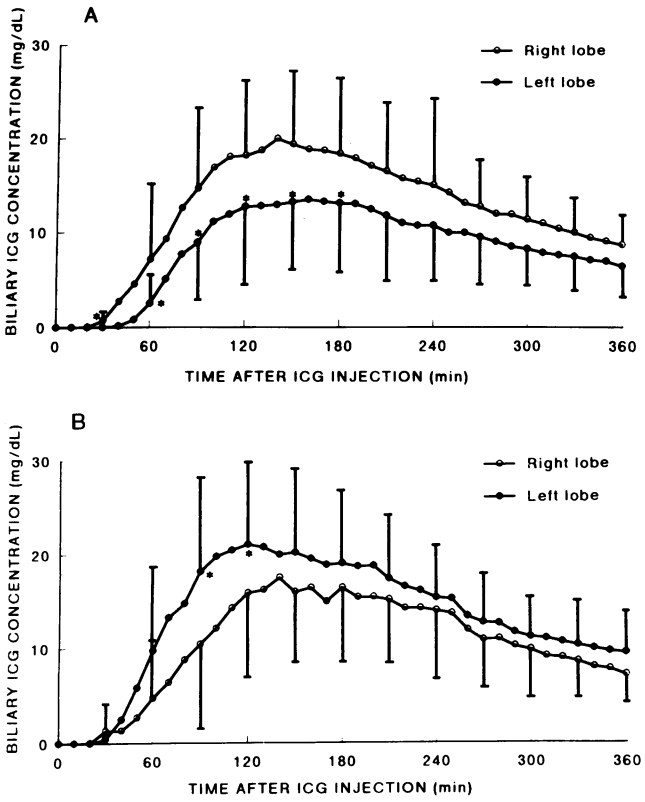

Figure 2. Biliary ICG concentration curves against time (A) before and (B) after RPE. (*)$p < 0.05$ *vs.* right lobe by Mann–Whitney test.

total ICG excretion, and L_{VOL}, defined as the percentage of the left lobar volume to the total liver volume. L_{ICG} was significantly increased, from 35.0 ± 6.6% before RPE to 55.1 ± 11.6% after RPE ($p < 0.05$), with a mean increase of 20.1%. L_{VOL} also exhibited a significant increase, from 34.4 ± 5.0% before RPE to 42.7 ± 6.5% after RPE, with a mean increase of 8.3% (Fig. 4). Regression and correlation analyses demonstrated a close correlation between L_{VOL} and L_{ICG} before RPE ($r = 0.9082$, $p < 0.005$) with a regression slope of 1.2 (Fig. 5). After RPE, however, no significant correlation was observed.

DISCUSSION

In the current study, we have demonstrated that RPE results in enhancement of the functional capacity as well as the volume of the left (nonembolized) lobe. The relative functional capacity of the left lobe increased by 20.1% to 55.1% 11 days after RPE. This increase was greater than that observed in the relative size of the left lobe (8.3%). We reported that the relative size of the left lobe increases by 12% 11 to 13 days after RPE.[10,16] The smaller increase in the left lobar volume in the current study occurred because half of the subjects had diabetes mellitus.[16] The total function and volume of the liver did not change after RPE, thus indicating that the function and volume of the right (embolized) lobe and the left (nonembolized) lobe were in balance. This confirms the belief that preoperative portal vein embolization increases the safety of surgery in terms of liver function and not just hepatic volume.

Indocyanine green, a tricarbocyanine dye, has been used widely for evaluation of liver function and hepatic blood flow.[17–20] Indocyanine green is removed from the blood solely by the liver and is excreted into the bile without biotransformation.[19] These unique characteristics enabled us to assess hepatic lobar function by measuring biliary ICG excretion in patients with complete biliary obstruction of the hepatic hilus. In the transhepatic transport system of ICG, hepatic uptake of the dye occurs through the actions of a flow-limited mechanism associated with limited energy, whereas excretion across the canalicular membrane is the rate-limiting step.[21] Because bile excretion involves an adenosine triphosphate (ATP)–utilizing reaction and the bile flow rate reflects the cellular level of ATP,[22] biliary ICG excretion is regulated by the cellular ATP level. Synthesis of ATP is controlled by liver mitochondrial function, which is the most important functional reserve of the liver.[23,24] Therefore, the capacity to excrete ICG appears to accurately reflect liver function. Kawamoto et al.[21] showed a marked decrease in ICG excretion without a decrease in ICG uptake after only 20 minutes of liver ischemia in the rat. They stressed that biliary ICG excretion, not hepatic uptake, was a good indicator of liver function. Increased ATP synthesis in the nonligated lobes with decreased ATP synthesis in the ligated lobes was reported in rabbit[25] and rat[26] models after portal vein branch ligation. In the current study, RPE increased bile volume and elevated biliary ICG concentration in the left (nonembolized) lobe. This resulted in a significant increase (20.1%) in ICG excretion in the left lobe. The functional reserve of the left lobe, therefore, was increased by enhancement of mitochondrial function.

The pharmacokinetics of ICG in our postjaundice patients revealed that K_{ICG} and K_{12}, parameters representing total hepatic uptake of ICG, were considerably elevated after RPE, although the differences were not significant. Researchers have reported that full recovery of liver function after relief of obstructive jaundice lags behind improvements in total bilirubin concentration.[27,28] In patients without jaundice, a slight deterioration in K_{ICG} after RPE has been reported.[29] These findings suggest that the liver is injured by RPE but that RPE's influence on total liver function is minimal. In addition, RPE does not impede biliary decompression by percutaneous transhepatic biliary drainage. K_{el} did not significantly change after RPE, which was consistent with the total ICG excretion results. Meijer et al.[30] have shown

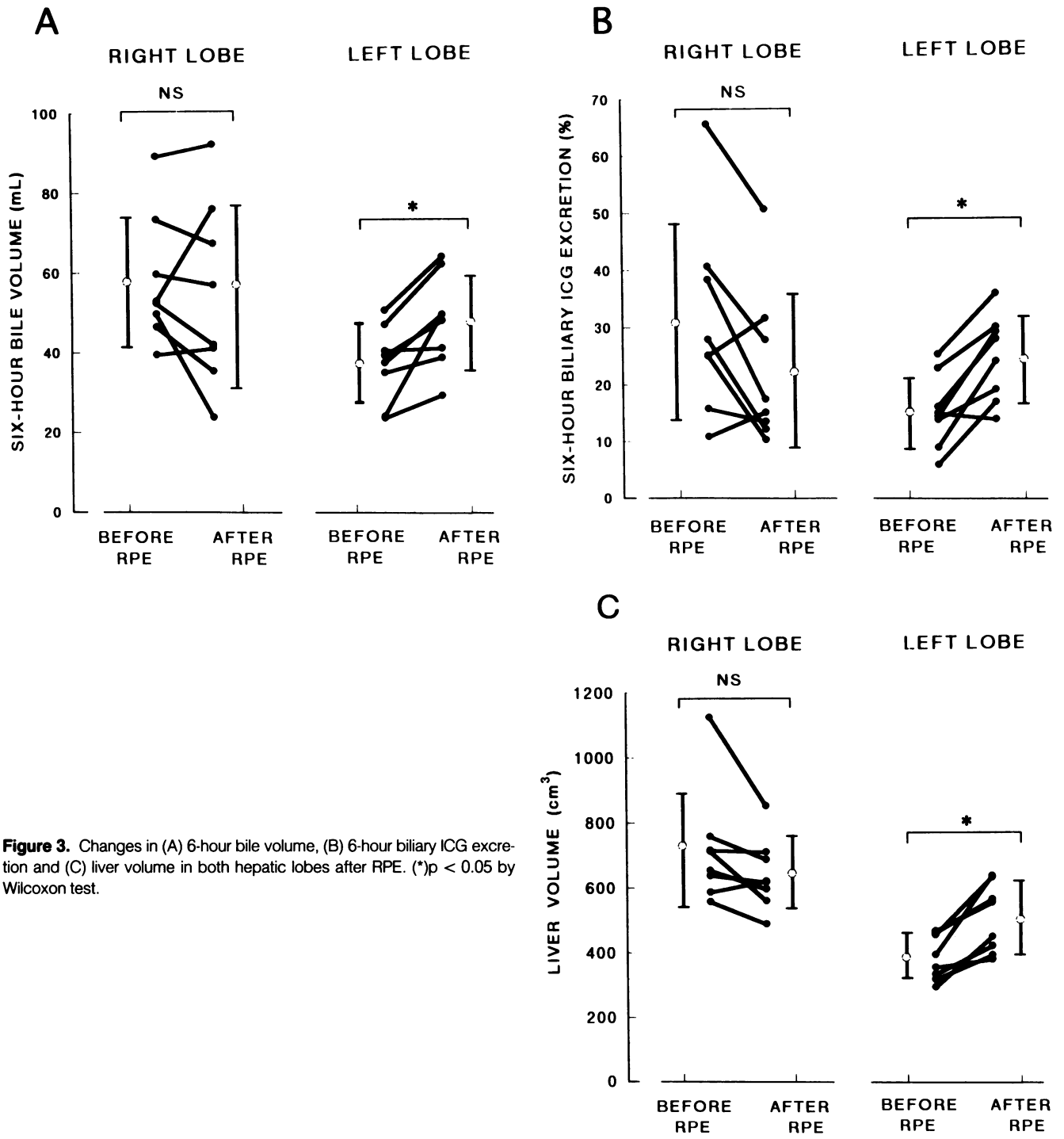

Figure 3. Changes in (A) 6-hour bile volume, (B) 6-hour biliary ICG excretion and (C) liver volume in both hepatic lobes after RPE. (*)$p < 0.05$ by Wilcoxon test.

that the biliary excretion of ICG in healthy subjects could be quantified using a two-compartment pharmacokinetic analysis of plasma disappearance curves. In our small series, however, no correlation between K_{el} and ICG excretion was found (data not shown). Therefore, it remains unknown whether, in postjaundice patients, K_{el} represents actual biliary ICG excretion.

Before RPE was performed, L_{ICG} and L_{VOL} were significantly correlated, with a regression slope of approximately one. This finding demonstrates one-to-one correspondence between function and volume, that is, in terms of functional capacity per liver volume in healthy subjects, the left lobe is almost equal to the right lobe. After RPE was performed, however, no correlation was

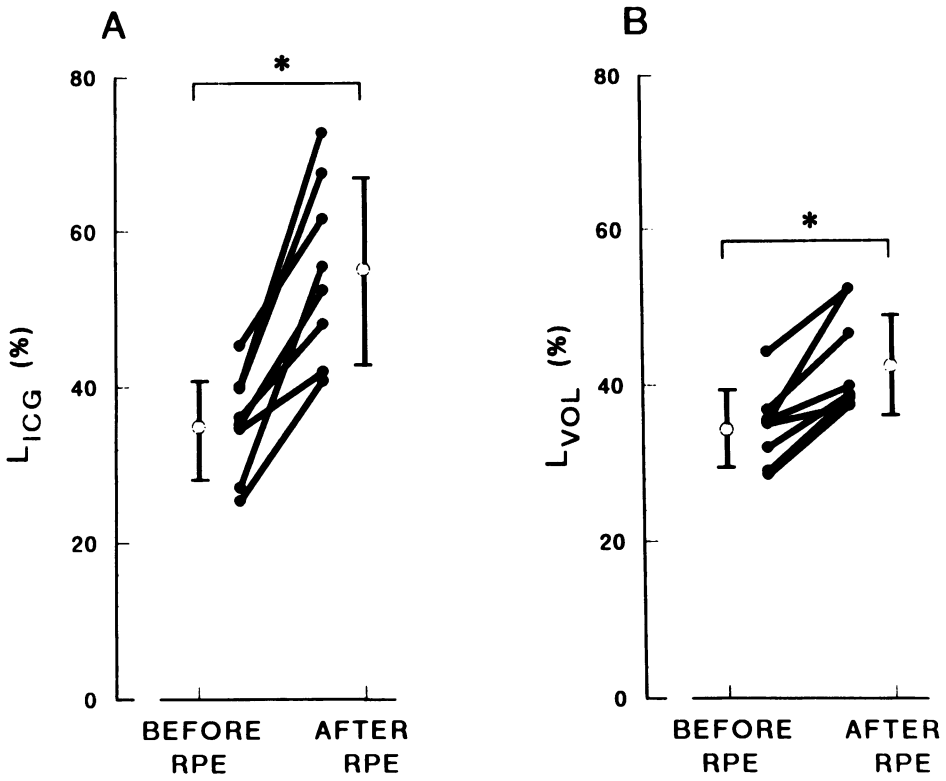

Figure 4. Changes in the percentage of (A) ICG excretion in the left lobe to the whole-liver ICG excretion (L_{ICG}) and of (B) left lobar volume to the entire liver volume (L_{VOL}) after RPE. (*)$p < 0.05$ by Wilcoxon test.

observed: the extent of L_{ICG} gain differed from the extent of L_{VOL} gain in each patient, and the former was higher than the latter in all of the subjects. This suggests that, in a relatively early stage after RPE, the functional gain in the left (nonembolized) lobe is more rapid and of a greater magnitude than the volume gain. We observed that the increase in the left lobar volume after RPE continued for at least 1 month.[16] However, it remains unknown whether, in later stages, the volume gain will catch up with the functional gain.

In conclusion, measurement of biliary ICG excretion is clinically useful for estimating changes of hepatic lobar function and has revealed that RPE contributes to a movement of 20.1% of the functional capacity of the liver from the right to the left lobes 11 days after the procedure without affecting total liver function.

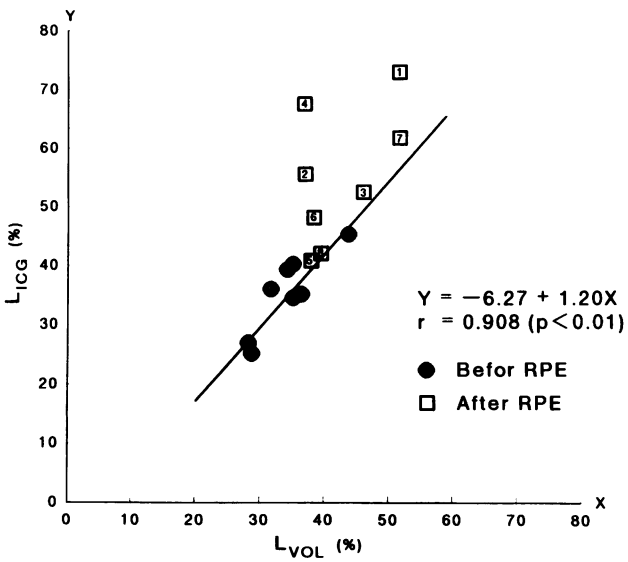

Figure 5. Correlation between the percentage of the left lobar volume to the entire liver volume (L_{VOL}) and the percentage of biliary ICG excretion in the left lobe to the whole-liver ICG excretion (L_{ICG}). (Numbers in black circles and squares) Patient numbers. (Solid line) Regression line in patients before RPE.

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